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CORRESPONDENCE

Letters to the Editor

Statins and Altered Glucose Metabolism

A Laboratory Curiosity or a New Disease?

Koh et al. (1), in a small number of patients given atorvastatin, showed that despite reductions in low-density lipoprotein cholesterol, atorvastatin treatment resulted in significant increases in fasting insulin and glycated hemoglobin levels consistent with insulin resistance in patients with hypercholesterolemia. These results are in agreement with our studies in 345,417 veteran patients (mean age 61 years; 94% men; 6% with diabetes), which showed that in patients without diabetes as well as those with diabetes, fasting blood sugar increased with the use of any statin ($p < 0.0001$) (2). After adjustment for age and the use of aspirin, beta-blockers, and angiotensin-converting enzyme inhibitors, the change in fasting blood sugar in patients without diabetes using statins was 7 mg/dl (vs. 5 mg/dl in patients not using statins; $p < 0.0001$), and for patients with diabetes using statins, it was 39 mg/dl (vs. 32 mg/dl in patients not using statins; $p < 0.0001$).

Sattar et al. (3) found a small but significant increase in diabetes in patients taking statins in an analysis of the results of several randomized controlled trials of statins.

The mechanisms by which statins may influence glucose metabolism are unclear. We suggested that statins may alter glycemic control by decreasing various metabolites, such as isoprenoid, farnesyl pyrophosphate, geranylgeranyl pyrophosphate, and ubiquinone, which enhance glucose uptake via glucose transporter type 4 in adipocytes and impair insulin release (2).

However, further work needs to be done to define the following: 1) Are the outcomes of patients who develop diabetes on statins different from those who do not? In other words, is the rise in fasting blood sugar just a laboratory curiosity or a real disease? 2) Do patients who develop diabetes need to be treated similarly as those who develop diabetes while not taking statins? 3) How soon after starting statins does altered glucose metabolism become evident? 4) Is the altered glucose metabolism related to the dose of statins? and 5) What is the precise mechanism of altered glucose metabolism?

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Reply

We thank Dr. Mehta for commenting on our study (1). We agree that it is of significant clinical interest to understand potential mechanisms by which some statins have detrimental effects on glucose homeostasis whereas other statins improve the metabolic phenotype. Sukhija et al. (2) suggested that statins alter glycemic control by decreasing various isoprenoids that enhance glucose uptake via glucose transporter type 4 in adipocytes and contribute to insulin release.

Recent experimental studies have demonstrated that compared with hydrophilic statins, lipophilic statins have pleiotropic actions that cause unfavorable metabolic effects, such as reduction of insulin secretion and exacerbation of insulin resistance (3,4). Sattar et al. (5) showed that risk for the development of diabetes with statins is highest in older participants, while trials with pravastatin have reduced the development of diabetes in participants below a mean age of 65 years. We previously observed that pravastatin improves insulin sensitivity, whereas simvastatin worsens insulin resistance despite comparable improvements in lipid profiles and endothelium-dependent vasodilation in patients with hypercholesterolemia (6). These differential metabolic actions of lipophilic and hydrophilic statins are consistent with recent meta-analyses (7). Among plausible mechanisms that deserve further investigation are potential central nervous system actions of lipophilic statins to impair glucose homeostasis.

Certainly, mechanisms by which atorvastatin treatment results in increased fasting insulin and glycated hemoglobin levels require further investigation. Our observations are consistent with analyses of atorvastatin therapy and the incidence of diabetes (8). It is particularly important to investigate mechanisms of differential metabolic effects of various statins in patients at risk for metabolic diseases, including diabetes, obesity, and metabolic syndrome.

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